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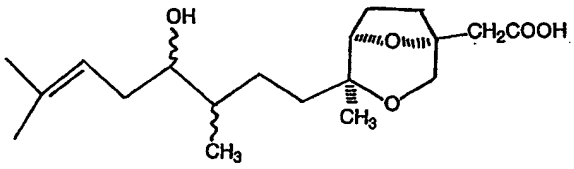
(54) Total synthesis of 1RS,4SR,5RS-4-(4,8-dimethyl-5-hydroxy-7-nonen-1-yl)-4-methyl-3,8-dioxabicyclo(3.2.1)octane-1-acetic acid and related compounds.

(57) The synthesis of 1RS, 4SR, 5RS-4-(4,8-dimethyl-5-hydroxy-7-nonen-1-yl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetic acid



and related compounds is described and their pharmacological activities are described.

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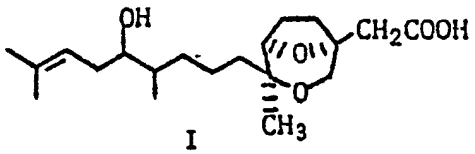
Total Synthesis of 1RS,4SR,5RS-4-(4,8-dimethyl-5-hydroxy-7-nonen-1-yl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetic acid and Related Compounds

The isolation and structural determination of zoapatanol, 2S,3R,6E-(2"-hydroxyethylidene)-2-methyl-2-(4',8'-dimethyl-5'-oxo-7'-nonenyl)-oxepan-3-ol, one of the active ingredients in the zoapatle plant, is described in U.S. Patent No. 4,086,358, issued April 25, 1978. In U.S. Patent No. 4,102,895, issued July 25, 1978, the preparation of 1RS,4SR,5RS-4-(4,8-dimethyl-5-hydroxy-7-nonen-1-yl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetic acid, a compound derived from zoapatanol, is described. The bicyclic derivative has the following formula:



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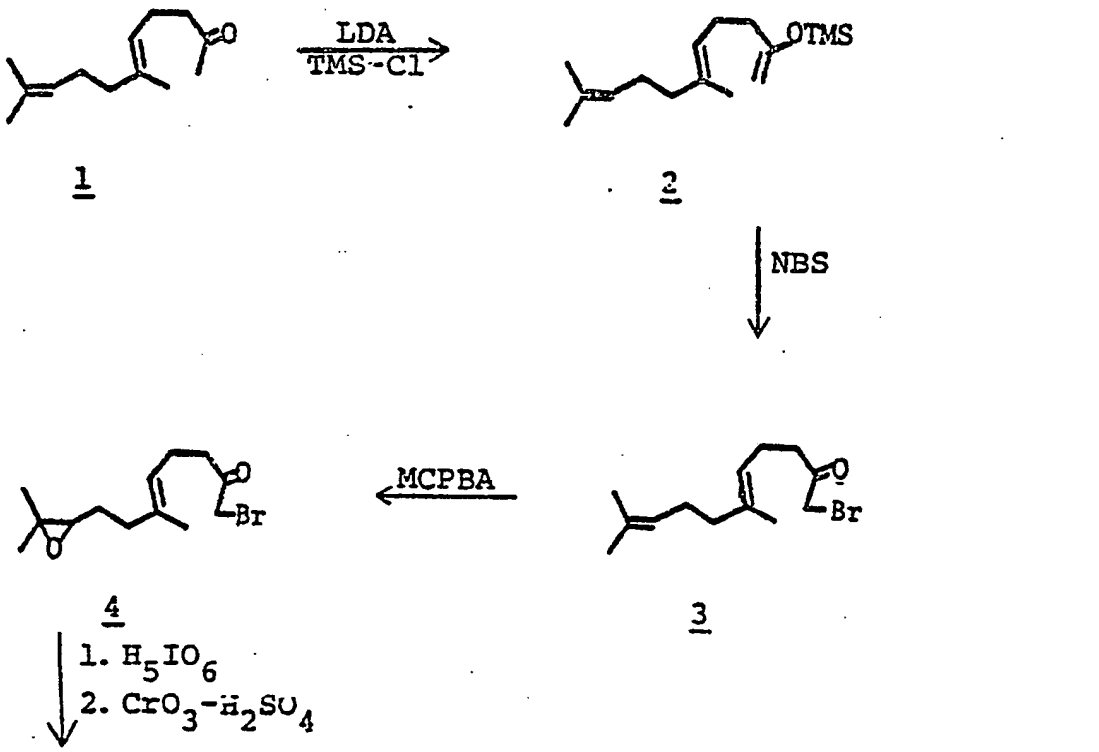
The present invention relates to a method of synthesizing 1RS,4SR,5RS-4-(4,8-dimethyl-5-hydroxy-7-nonen-1-yl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetic acid. This acetic acid derivative is active as a utero-evacuant agent. Many of the intermediates employed in the synthesis are novel compounds and are included as part of the invention.

The synthesis is comprised of several steps which are summarized in the following schematic diagram:



1

2

4

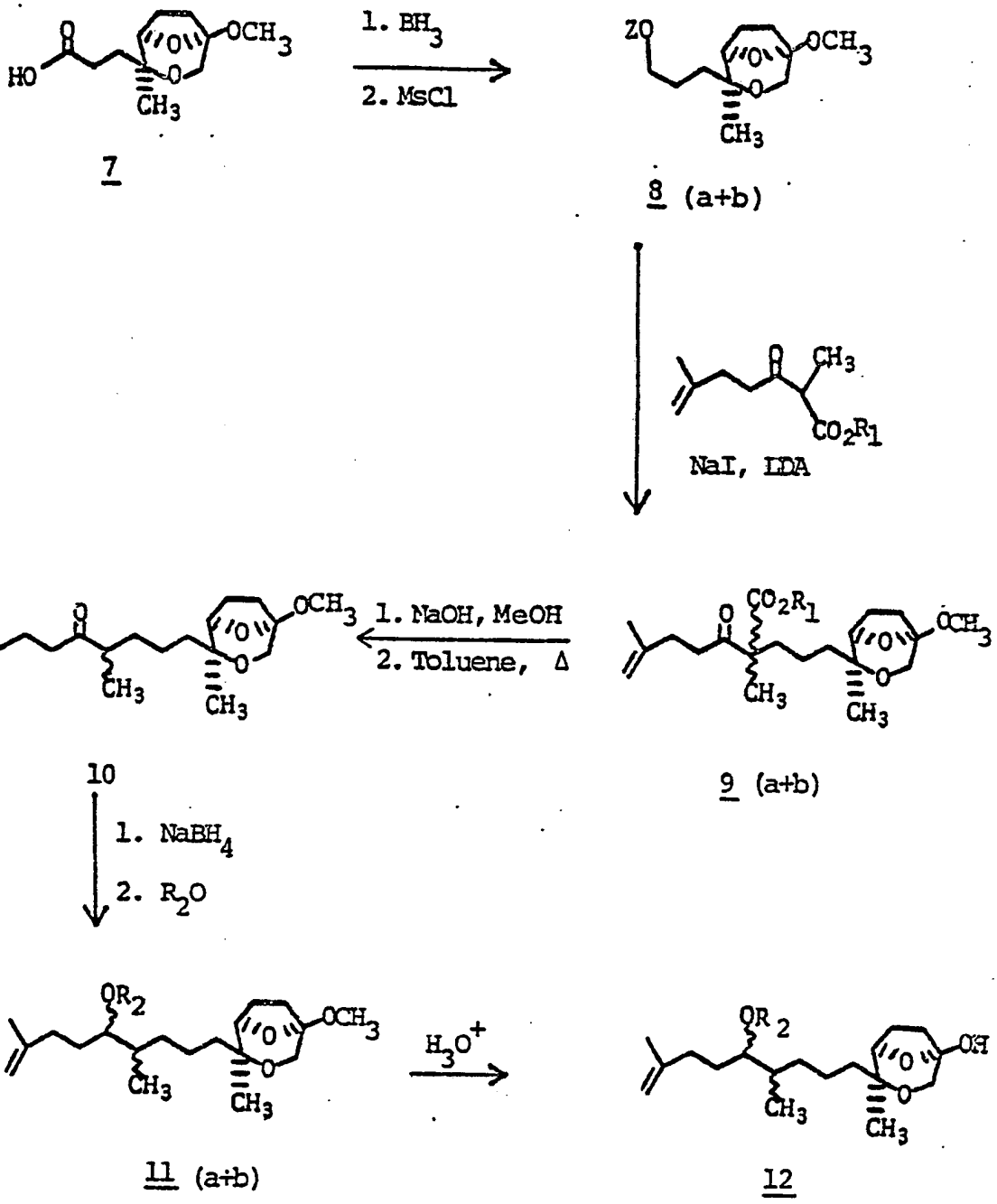
3

5 (a+b)

6a

7

6b + 6c



7

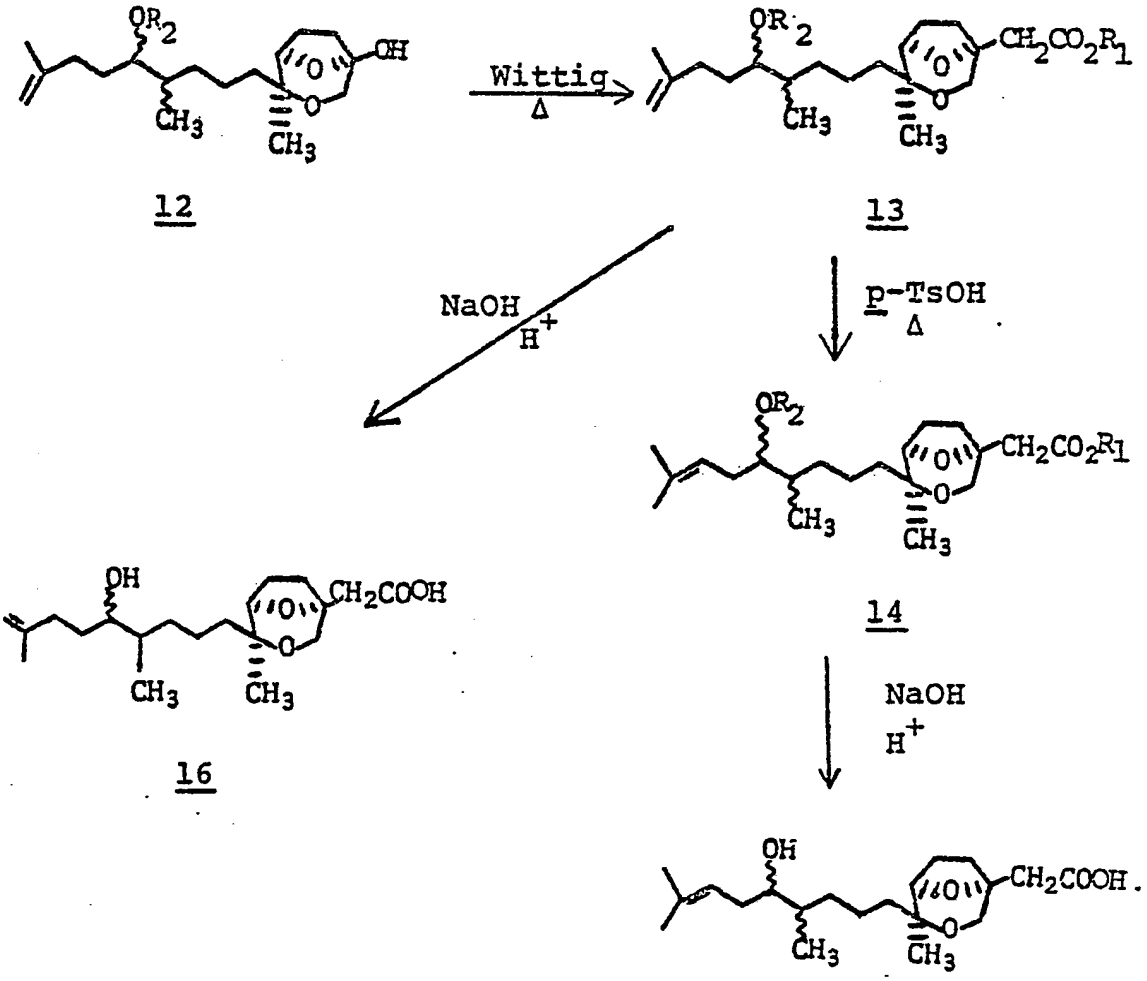
8 (a+b)

9 (a+b)

10

11 (a+b)

12


OR2
OH
CH3
CH3
Wittig
Δ
CH2CO2R1
12
13
NaOH
H+
p-TsOH
Δ
14
CH2COOH
16
NaOH
H+
I

wherein X is hydrogen or hydroxy; Z is hydrogen or a mesyl group, R_1 is hydrogen or a lower alkyl group having 1-5 carbon atoms, R_2 is hydrogen or a lower acyl group having 2-5 carbon atoms, LDA is lithium diisopropylamide, TMS is trimethylsilyl group, NBS is N-bromosuccinimide and MCPBA is m-chloroperoxybenzoic acid.

As can be seen from the diagram, the first step in the synthesis involves the preparation of an enol silyl ether (2) by the reaction of geranyl acetone (1) with trimethylsilyl chloride in the presence of lithium diisopropylamide in a suitable solvent. The reaction is carried out preferably at a temperature between -80°C and +15°C. The preferred reaction temperature is -70°C. Suitable solvents which can be employed include tetrahydrofuran, dioxane, diethyl ether and dimethoxyethane. The starting material (1) is prepared by the method of Stork & Burgstahler [Stork, G. and Burgstahler, A.W., J. Amer. Chem. Soc., 77, 5068 (1955)]. The enol silyl ether (2) is then reacted with a brominating agent such as N-bromosuccinimide to form the bromo-ketone (3). The reaction is carried out preferably at a temperature between -80°C and 0°C. The preferred temperature is about -78°C. As the solvent for the reaction tetrahydrofuran, dioxane diethyl ether and dimethoxyethane may be employed. Farnesol, citral, pseudoionine or linalool can also be employed as the starting material in the synthesis since they can be converted to geranyl acetone or one or more intermediates in the synthesis such as the bromo keto acid and aldehyde (5a and 5b).

The terminal double bond in the bromo-ketone (3) is then converted to the epoxide (4) by reaction with a peroxy acid such as, for example, m-chloroperoxybenzoic acid, peracetic acid, permaleic acid, perbenzoic acid,

perphthalic acid and pertrifluroacetic acid in a suitable solvent such as, for example, methylene chloride, chloroform, and diethyl ether. The reaction is generally carried out at a temperature between -10° and 20°C. The preferred reaction temperature is 0°C although room temperature may also be employed. The epoxide (4) is then converted to the corresponding aldehyde (5a, X=H) by reaction with periodic acid in an aqueous medium such as aqueous tetrahydrofuran, dioxane and dimethyoxyethane. Reaction of the aldehyde (5a) with Jones reagent yields the corresponding carboxylic acid (5b). The oxidation is carried out at a temperature between -10°C and room temperature in a suitable solvent such as acetone, methylene chloride and chloroform. The preferred reaction temperature is 0°C. The acid is separated from the reaction mixture by techniques known to those skilled in the art.

The bromo-keto acid (5b) is converted to the cis-bromo hemiketal γ-lactone (6a) by reaction with a peroxy acid such as, for example, m-chloroperoxybenzoic acid, perbenzoic acid and perphthalic acid. The reaction is carried out at a temperature between 0°C and room temperature in a suitable solvent such as, for example, methylene chloride, chloroform and ether. The preferred reaction temperature is about 2°C. The residue containing the cis-bromohemiketal γ-lactone (6a) is converted to a mixture of cis and trans ketals (6b and 6c) by reaction with trialkyl orthoformate such as trimethyl orthoformate and triethyl orthoformate in the presence of a strong anhydrous acid such as, for example, sulfuric acid, phosphoric acid, potassium acid sulfate and p-toluene sulfonic acid in an alcohol such as, for example, methanol or ethanol. The reaction can be carried out at a temperature between 0°C and room temperature. The preferred temperature range is about 2° - 5°C. The reaction can also be carried out in the absence of the trialkyl orthoformate.

The cis-bromo ketal (6b) in the mixture of cis/trans-bromo ketals (6b and 6c) is converted to the bicyclic ketal acid (7) by reaction with an alkaline hydroxide such as sodium hydroxide or potassium hydroxide in a highly polar aprotic solvent such as, for example, dimethylsulfoxide. The bicyclic ketal-acid (7) is converted to the 2-hydroxyethyl-3,8-dioxabicyclo[3.2.1]octane (8a, Z=H) by reaction with borane in a suitable solvent such as tetrahydrofuran. The reaction can be carried out at a temperature between 0°C and room temperature. The bicyclic ketal mesylate (8b, Z=mesyl) is prepared by reacting the bicyclic hydroxyethyl compound (8a) with methanesulfonyl chloride in the presence of a tertiary amine such as, for example, triethylamine and pyridine. The reaction can be carried out at a temperature between 0°C and room temperature. The preferred temperature range is about 0°C to 5°C.

The bicyclic ketal mesylate (8b) is converted to the nonenyl-3,8-dioxabicyclo[3.2.1]octane (9a, R_1=alkyl) by first converting it to a halo derivative by reaction with a halide such as sodium iodide or lithium bromide and then reacting the halo derivative with ethyl 2,6-dimethyl-3-oxo-6-heptenoate in the presence of a strong alkali metal base such as sodium hydride, lithium diisopropylamide, potassium t-butoxide, sodamide, sodium methoxide and sodium ethoxide, for example, in a suitable solvent such as tetrahydrofuran dioxane, diethyl ether and dimethoxyethane.

The reaction is carried out at a temperature between 0°C and room temperature. The preferred temperature range is 0°C to 10°C. After removal of the solvents, anhydrous dimethylformamide is added to the reaction mixture and the -keto ester (9a, R_1=alkyl) is separated from the

reaction mixture by techniques known to those skilled in the art.

The β-keto ester (9a) is then stirred in a basic aqueous-alcoholic solution until decarboxylation is achieved which results in the formation of the ketone (10). As the base an aqueous hydroxide such as aqueous sodium hydroxide or potassium hydroxide may be employed. The preferred alcohol is methanol. The β-keto acid (9b, R=H) obtained in part is decarboxylated to 9a by heating in a solvent such as toluene, benzene or cymene.

The ketone (10) is reduced to the corresponding alcohol (11a, R_2=H) by reduction with a ketone reducing agent such as sodium borohydride, lithium borohydride and lithium aluminum hydride in a suitable solvent such as, for example, ethanol, tetrahydrofuran and methanol. The reaction can be carried out at a temperature between 0°C and room temperature. The preferred temperature range is 0°C to 5°C.

The alcohol (11a) is converted to the corresponding ester (11b) by reaction with a carboxylic acid anhydride or acyl halide such as, for example, acetic anhydride, propionic anhydride, butyric anhydride, acetyl chloride, benzoyl chloride, etc., in the presence of a base such as pyridine or trimethylamine.

The hemiketal (12) is prepared by treating the ketal (11b) with a strong acid such as aqueous hydrochloric acid, sulfuric acid and phosphoric acid in a suitable solvent such as acetone, tetrahydrofuran or dioxane. The reaction is preferably carried out at a temperature between 30°C and 60°C, although room temperature may also be employed.

The attachment of the last two carbon atoms in the structure of the zoapatanol derivative is accomplished by means of a Wittig reaction on the hemiketal (12) with (carbethoxymethylene)triphenylphosphorane at elevated temperatures to afford the ester (13). The reaction can be carried out at a temperature between 90°C and 150°C, however, the preferred temperature range is 110°C to 130°C.

Isomerization of the double bond in the side chain of the ester (13) to the 7-nonenyl isomer (14) is accomplished by treating the ester (13) with p-toluenesulfonic acid in a hydrocarbon solvent such as benzene or toluene. The reaction is preferably carried out at the reflux temperature of the solvent. The free acid (15), which is the subject of this invention is obtained by hydrolysis of the ester (14) according to techniques known to those skilled in the art.

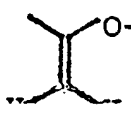
Hydrolysis of the bicyclic ester (13) in a basic aqueous-alcoholic medium yields the free acid (16) which is the terminal double bond isomer of the zoapatanol derivative (15). Bases such as sodium hydroxide and potassium hydroxide may be employed. As the alcohol, ethanol, methanol and propanol may be employed. The isomer (16) possesses contragestational activity.

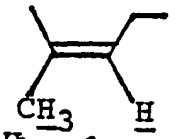
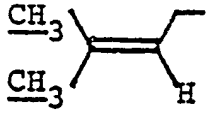
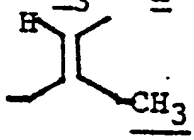
The following examples describe the invention in greater detail and are intended to be a way of illustrating but not limiting the invention.

Example 1

6,10-Dimethyl-2-trimethylsilyloxy-5(E)-1,5,9-undecatriene (2)

Triphenylmethane indicator (50 mg) is added to diisopropylamine (distilled from lithium aluminum hydride; 6.5 mg, 0.046 M) dissolved in tetrahydrofuran (distilled from lithium aluminum hydride; 60 ml). The solution is cooled to -10°C (ice-methanol bath), and n-butyllithium in hexane (18.7 ml of 2.4 M, 0.044M) is added while stirring at -10°C. The resulting solution is kept at -10°C for 20 minutes, and then at -70°C for an additional 20 minutes. While stirring at -70°C, geranyl acetone (6.2 g, 0.032 M) dissolved in anhydrous tetrahydrofuran (6.0 ml) is added within about 15 minutes to the above solution followed by the addition via a cannula of a freshly prepared mixture of trimethylsilyl chloride (15 ml, 0.118 M) and triethylamine (2.6 ml, 0.018 M) in tetrahydrofuran (20 ml). After keeping the reaction mixture at -70°C for 1.5 hours, solid $NaHCO_3$ is added, followed by a saturated aqueous $NaHCO_3$ solution (70 ml), also added at -70°C. During this addition, the temperature quickly rises to -10°C and it is held at -10°C with a dry ice-acetone bath. After the addition of the $NaHCO_3$ solution, the cooling bath is removed and a water bath is substituted. The two layers are separated and the aqueous layer is re-extracted with ether. The ether extracts are combined with the tetrahydrofuran layer and the solution is washed with saturated aqueous NaCl solution, dried with Na_2SO_4, filtered and evaporated in vacuo to afford crude 6,10-dimethyl-2-trimethylsilyloxy-5(E)-1,5,9-undecatriene (8.7 g) as a mobile yellow oil.

TLC (CH_2Cl_2): R_f = 0.95; IR (neat): 1647, 1620, 1253, 849 cm^{-1}; NMR ($CDCl_3$ δ): 5.10 (m, 2H. olefinic protons); 4.02 (s, 2H,  ; 2.03 (m, 8H, $-CH_2-CH_2-$);

1.68 (br. s, 3H, ); 1.62 (br sm 6H,  , ).

Example 2

1-Bromo-6,10-dimethyl-5(E)-5,10-undecadien-2-one (3)

Anhydrous solid $NaHCO_3$ (3.3 g) is added to crude 6,10-dimethyl-2-trimethylsilyloxy-5(E)-1,5,9-undecatriene (8.7 g, 0.032 M) dissolved in tetrahydrofuran (170 ml) with stirring. The mixture is cooled to -78°C under nitrogen, and solid N-bromosuccinimide (6.04 g, 0.034 M) is added. The reaction mixture is stirred at -78°C for 2 hours and then poured into a stirred mixture of ice-cold 10% aqueous $NaHCO_3$ solution and ether. The organic layer is separated, washed with 10% aqueous Na_2SO_4 solution, saturated, aqueous NaCl, dried with Na_2SO_4, filtered and evaporated in vacuo to afford 1-bromo-6,10-dimethyl-5(E)-5,10-undecadien-2-one as a brown oil (8.6 g, 98.4%).

TLC (CH_2Cl_2): R_f = 0.90; IR (neat): 1724, 845 cm^{-1}: NMR ($CDCl_3$, δ): 5.01 (m, 2H, vinyl protons); 3.85 (s, 2H, $-\overset{O}{\overset{\|}{C}}-\underline{CH_2}-Br$): 2.55 (m, 2H, $-\underline{CH_2}-\overset{O}{\overset{\|}{C}}-CH_2-Br$); 2.28-1.96 (m, 6H, methylenes allylic to double bond); 1.66 (m, 3H, cis vinyl methyl); 1.61 (m, 6H, trans vinyl methyls).

Example 3

1-Bromo-6,10-dimethyl-9,10-oxido-5(E)-undecen-2-one (4)

Water (250 ml) and saturated $NaHCO_3$-H_2O (250 ml) are added to 1-bromo-6,10-dimethyl-5(E)-5,10-undecadien-2-one (31.5 g, 0.115 M) dissolved in CH_2Cl_2 (500 ml). A solution of m-chloroperoxybenzoic acid (MCPBA; 22.0 g, 0.127 M) dissolved in CH_2Cl_2 (500 ml) is added to the

stirred mixture at +20°C dropwise within 3 hours. The CH_2Cl_2 layer is separated, washed with $NaCl-H_2O$, dried with Na_2SO_4, filtered and evaporated in vacuo to afford crude 1-bromo-6,10-dimethyl-9,10-oxido-5(E)-undecen-2-one (33.3 g).

TLC (Et_2O): R_f = 0.77
NMR ($CDCl_3$, δ): 5.08 (m, 1H, vinyl proton); 3.87 (s, 2H, $-\overset{\overset{O}{\|}}{C}-CH_2-Br$); 2.68 (t, 1H, 9-H); 1.67 (br. s, 3H, 6(E)CH_3); 1.30 (s, 3H, 10(Z)CH_3); 1.27 (s, 3H, 10(E)CH_3).

The crude product is used without further purification in the next step.

Example 4

1-Bromo-6-methyl-2-oxo-5(E)-nonen-9-al (5a)

Periodic acid (34.6 g, 3x0.051 M) dissolved in aqueous tetrahydrofuran (240 ml, 5% by volume) is added to crude 1-bromo-6,10-dimethyl-9,10-oxido-5(E)-undecen-2-one (14.7 g, 0.051 M) in aqueous tetrahydrofuran (240 ml, 5% by volume) while stirring at 20°C over a 3 minute period and the mixture is stirred at 20°C for an additional 9 minutes. The reaction mixture is then added to a stirred mixture of ice cold saturated $NaHCO_3-H_2O$ (400 ml) and ether (700 ml). The mixture is filtered, the organic layer is separated, washed with 10% $NaHCO_3-H_2O$, $NaCl-H_2O$, dried with Na_2SO_4, filtered and concentrated in vacuo to give crude 1-bromo-6-methyl-2-oxo-5(E)-nonen-9-al (14.5 g).

TLC (10% ether in CH_2Cl_2): R_f = 0.52
IR (neat): 2730 (CH of aldehyde), 1706 cm^{-1} (broad CO groups).
The crude reaction product is used without further purification in the next step.

Example 5

1-Bromo-6-methyl-2-oxo-5(E)-nonen-9-oic acid (5b)

Jones reagent (20 ml) is added to 1-bromo-6-methyl-2-oxo-5(E)-nonen-9-al (14.5 g, 0.059 M of ~38% pure) in acetone (250 ml) within 5 minutes while stirring at 0°C. The resultant solution is stirred for an additional 10 minutes at 0°C and then added to a stirred solution of ice cold saturated $NaHCO_3$-H_2O (350 ml). The acetone is removed in vacuo, CH_2Cl_2 (300 ml) is added, and the mixture is filtered. The organic phase is washed with H_2O and then added to the $NaHCO_3$-H_2O. The aqueous basic solution is washed once with CH_2Cl_2 and once with ether, stirred at 0°C and acidified carefully with ice cold 6N HCl-H_2O to pH = 2.0. The acidic solution is then extracted twice with CH_2Cl_2 and once with ether. The extracts are washed separately with NaCl-H_2O, combined, dried with Na_2SO_4, filtered, and evaporated in vacuo to give 1-bromo-6-methyl-2-oxo-5(E)-nonen-9-oic acid (3.92 g, 29.3%). The compound solidifies on standing.

TLC (Et_2O): R_f = 0.67; IR (neat): 2700-2330 (OH), 1710 cm^{-1} (CO). NMR ($CDCl_3$, δ): 8.67 (br, 1H, $-CO_2\underline{H}$), 5.17 (t, 1H, vinylic H), 3.88 (s, 2H, $-CO-\underline{CH_2}-Br$), 1.67 (br. s, 3H, vinylic $C\underline{H_3}$).

Example 6

Cis/trans 2-(2-bromomethyl-2-methoxytetrahydrofuran-5-yl-2-methyl-5-oxotetrahydrofuran (6b and 6c)

Metachloroperoxybenzoic acid (1.40 g, 8.1 mM) in CH_2Cl_2 (20 ml) is added to 1-bromo-6-methyl-2-oxo-5(E)-nonen-9-oic acid (2.2 g, 8.4 mM) in CH_2Cl_2 (15 ml) at 2°C dropwise, while stirring over a fifteen minute period. Stirring at 2°C is continued for three hours. Acetone (50 ml) and 0.2N HCl-H_2O (10 ml) are added at 2°C to the above stirred mixture and stirring is continued at approximately 5°C for 16 hours. The solvents are

evaporated in vacuo with no external heating. The residue is extracted with CH_2Cl_2 and the extract is washed with NaCl-H_2O containing enough $NaHCO_3$-H_2O to make it basic, and then with saturated NaCl-H_2O to a neutral pH. The extract is then dried with Na_2SO_4, filtered, and evaporated in vacuo to give an oily solid (3.9 g). A small sample of the mixture is dissolved in CH_2Cl_2 and extracted twice with saturated $NaHCO_3$-H_2O. The extract is then washed with NaCl-H_2O, dried with Na_2SO_4, filtered and evaporated in vacuo to give the cis bromo hemiketal γ-lactone 2-(2-bromomethyl-2-hydroxytetrahydrofuran-5-yl)-2-methyl-5-oxotetrahydrofuran.

TLC (10% ether in CH_2Cl_2): R_f = 0.11. IR (neat): 3300 (OH), 1754 cm^{-1} (CO). NMR ($CDCl_3$, δ): 4.23 (m, 1H, H-C(O)CH_2-), 3.53 (s, 2H, -CH_2-Br), 2.05-3.00 (m, 8H, -CO-CH_2CH_2- and -CH_2CH_2-C(O)-O-), 1.38 (s, 3H, CH_3-).

The crude main batch (≈3.9 g) is dispersed in trimethyl orthoformate (4.0 ml). The dispersion is stirred under nitrogen at 2°C and ≈0.1 N H_2SO_4-methanol (1.4 ml of 0.27 ml conc. H_2SO_4 in 100 ml methanol) is added with a syringe through the serum cap. The reaction mixture is stirred at approximately 5°C for 2 days. The reaction mixture is then added dropwise to a stirred, ice cold mixture of saturated $NaHCO_3$-H_2O (20 ml) and CH_2Cl_2 (20 ml). The organic layer is washed with saturated $NaHCO_3$-H_2O, and then with NaCl-H_2O. It is then dried with Na_2SO_4, filtered, and concentrated in vacuo to give a mixture of cis/trans bromo ketal lactones 2-(2-bromomethyl-2-methoxytetrahydrofuran-5-

yl)-2-methyl-5-oxotetrahydrofuran (approximately 60/40 by GC/MS, 1.94 g).

TLC (10% Et_2O/CH_2Cl_2): R_f = 0.30. IR (neat): 1770 (broad), 1709 (sh), 1087, 1041 cm^{-1} (ether bonds).

NMR ($CDCl_3$,δ): 4.14 (m, 1H, H-C-O-), 3.64 (s, ∼60% of 2H, $-CH_2Br$), 3.49 (s, ∼40% of 2H, CH_2Br), 3.29 (s, ∼40% of 3H, $-OCH_3$), 3.23 (s, ∼60% of 2H, CH_2Br). GC/MS = two identical spectra, ratio ∼60/40. M^+ (292/294), $M^+ - OCH_3$ = 261/263. BP = 71 ($+O{=}C-CH_3$).

Example 7

1RS,4RS,5SR-4-(2-Carboxyethyl)-1-methoxy-4-methyl-3,8-dioxabicyclo[3.2.1]octane (7)

Potassium hydroxide pellets (6 g, 0.11 M) are added to the cis/trans mixture of the bromo ketal lactones (3.27 g, 11.2 mM) in anhydrous dimethylsulfoxide (25 ml). The mixture is stirred and heated at 45°C under nitrogen for three days. It is then cooled to room temperature and CH_2Cl_2 (100 ml) is added. The organic layer is decanted and the KOH pellets are quickly rinsed with ice water (60 ml). The rinse is added to the organic extract and the light yellow organic phase is re-extracted two times with ice water (2x20 ml) and then with NaCl-H_2O (20 ml). The dark, aqueous basic solution is cooled with ice water, stirred, acidified with 6N HCl-H_2O and the acidic solution is extracted with CH_2Cl_2 (∼50 ml). The aqueous layer is re-acidified with 2N HCl-H_2O (∼2.0 ml) and re-extracted with CH_2Cl_2 (2x50 ml). The CH_2Cl_2 extracts are combined and washed free of acid with NaCl-H_2O. The slightly turbid aqueous layer is re-extracted with ether and washed with NaCl-H_2O. The CH_2Cl_2 and ether solutions are combined, dried with Na_2SO_4, filtered, and evaporated in vacuo to give a mixture of 1RS,4RS,5SR-4-(2-carboxy-

ethyl)-1-methoxy-4-methyl-3,8-dioxabicyclo[3.2.1]octane and the non-cyclized trans bromo ketal lactone 2-(2-bromomethyl-2-methoxytetrahydrofuran-5-yl)-2-methyl-5-oxotetrahydrofuran (6c, 2.02 g of mixture). The mixture (2 g) is dissolved in ether (50 ml) and the ether solution is extracted with saturated $NaHCO_3$-H_2O (2x20 ml and 1x10 ml). The combined $NaHCO_3$-H_2O extracts are re-extracted with ether (3x20 ml). The combined ether extracts are evaporated in vacuo to give crude trans bromo ketal lactone (640 mg). The aqueous $NaHCO_3$-H_2O is re-extracted with CH_2Cl_2 and then with ether. These neutral CH_2Cl_2 and ether extracts are added to the crude residue obtained above and the solvent is evaporated in vacuo to give the crude trans bromo ketal lactone 2-(2-bromomethyl-2-methoxytetrahydrofuran-5-yl)-2-methyl-5-oxotetrahydrofuran (6c, 660 mg, 20%).

TLC (10% ether in CH_2Cl_2): R_f = 0.3. TLC (ether; R_f = 0.4. IR (neat) 1754 cm^{-1} (broad). NMR ($CDCl_3$,δ): 4.62 (t, J=8 Hz, 1H, ), 3.5 (q, J=12 Hz, 2H, ), 1.37 (s, 3H, ).

The $NaHCO_3$-H_2O extract is cooled with ice water, stirred, acidified carefully with 6N HCl-H_2O and then extracted with CH_2Cl_2 (2x50 ml) and ether (1x50 ml). The extracts are washed separately free of mineral acid with saturated NaCl-H_2O, combined, dried with Na_2SO_4, filtered, and evaporated in vacuo to give 1RS,4RS,5SR-4-(2-carboxyethyl)-1-methoxy-4-methyl-3,8-dioxabicyclo[3.2.1] octane (1.2 g, 46.6%), which solidifies on standing.

TLC (10% ether in CH_2Cl_2): R_f = 0.1. TLC (ether): R_f = 0.6. IR (neat) 2800-2500 (OH), 1715 (br, CO) cm^{-1}. NMR ($CDCl_3$,δ): 10.0 (br, 1H, $CO_2\underline{H}$), 3.93 (t, 1H, ), 3.53 (q, J=12 Hz, 2H, ), 3.43 (s, 3H, $-OCH_3$), 1.37 (s, 3H,). GC/MS of

TMS derivative (C.I. mode): $(M+1)^+$ 303; BP 213 (M+1-TMSOH).

Example 8

1RS,4RS,5SR-4-(2-Hydroxyethyl)-1-methoxy-4-methyl-3,8-dioxabicyclo[3.2.1]octane (8a)

$BH_3 \cdot THF$ (20 ml of approximately 1 molar solution) is added to 1RS,4RS,5SR-4-(2-carboxyethyl)-1-methoxy-4-methyl-3,8-dioxabicyclo[3.2.1]octane (3.13 g, 13.6mM) in anhydrous tetrahydrofuran (30 ml) while stirring at 2°C under nitrogen within three minutes. Stirring is continued for thirty minutes at 2°C and at room temperature for two hours after which the solution is added dropwise, carefully, while stirring, to ice water (20 ml). The aqueous solution is extracted with CH_2Cl_2 and with ether and the combined extracts are concentrated in vacuo. The residue is dissolved in CH_2Cl_2 and the solution is washed with saturated NaCl-H_2O containing enough saturated $NaHCO_3$-H_2O to make it basic. The extract is washed with saturated NaCl-H_2O, dried with Na_2SO_4, filtered, and evaporated in vacuo to give 1RS,4RS,5SR-4-(2-hydroxyethyl)-1-methoxy-4-methyl-3,8-dioxabicyclo[3.2.1]octane (2.94 g, 100%).

TLC (ether): R_f = 0.20. IR (neat) 3330 (OH), 1060 1040 cm^{-1} (ether bands). NMR ($CDCl_3$,δ): 3.92 (m, 1H, H-C(-)-O-), 3.63 (m, 2H, HO-CH_2-), 3.5 (q, 2H, -O-CH_2-C(O)-CCH_3): 3.40 (s, 3H, -OCH_3), 1.37 (s, 3H, -O-C(-)-CH_3). GC/MS: M^+216. BP 85 (+O=C(CH=CH)-OCH_3).

Example 9

1RS,4RS,5SR-4-(2-Methanesulfonyloxypropyl)-1-methoxy-4-methyl-3,8-dioxabicyclo[3.2.1]octane (8b)

Triethylamine (4.0 ml, 27 mM distilled, stored over CaH_2) is added to 1RS,4RS,5SR-4-(2-hydroxyethyl)-1-methoxy-4-methyl-3,8-dioxabicyclo[3.2.1]octane (2.94 g,

13.6 mM) in CH_2Cl_2 (30 ml). The resultant mixture is cooled with ice water, stirred under nitrogen and methanesulfonyl chloride (1.8 ml, 22.40 mM) is added dropwise within five minutes. The reaction mixture is stirred at 5°C under nitrogen for sixteen hours and then added dropwise to a stirred mixture of ice water (30 ml) and 2N HCl-H_2O (4.0 ml). The organic layer is separated, washed with saturated NaCl-H_2O (2x20 ml), dried with Na_2SO_4, filtered, and evaporated in vacuo to give 1RS,4RS,5SR-2-(2-methanesulfonyloxypropyl)-1-methoxy-4-methyl-3,8-dioxabicyclo[3.2.1]octane (3.29 g, 82.3%).

TLC (ether): R_f = 0.4. IR (neat): 1330, 1190, 1150 (OSO_2 bands), 1090, 1060 cm^{-1} (ether bands). NMR ($CDCl_3$,δ): 4.23 (m, 2H, $CH_3SO_2O-CH_2-CH_2-$), 3.87 (t, 1H, H-C-O), 3.53 (q, 2H, $-OCH_2-C(O)OCH_3$), 3.02 (s, 3H, CH_3SO_2O-). GC/MS: M^+ (294), $M^+ - CH_2O$ = 264, BP = 86 ($CH_2=C(CH_3)-OCH_3$).

Example 10

1RS,4RS,5SR-1-Methoxy-4-methyl-4-(4-carbethoxy-4,8-dimethyl-5-oxo-8-nonenyl)-3,8-dioxabicyclo[3.2.1] octane (9a)

The bicyclic ketal mesylate obtained in Example 9 above (458 mg, 1.56 mM) is added to sodium iodide (254 mg, 1.6 mM of Fisher, certified, with the exclusion of moisture, under nitrogen) followed by the addition of ethyl 2,6-dimethyl-3-oxo-6-heptenoate (0.75 ml, 3.0 mM). Anhydrous tetrahydrofuran (4 ml) is added to the slowly stirred mixture and the mixture is cooled to 0°C. A solution of lithium diisopropylamide in hexane (3 ml of approximately 0.7 molar = 2.1 mM) is added dropwise to this mixture under nitrogen. The mixture is allowed to come to 20°C and is stirred at room temperature for one day. The solvents are

removed by evaporation with a fast stream of nitrogen at room temperature. Anhydrous dimethylformamide (4.0 ml) is added to the residue and the stirring at room temperature under nitrogen is continued for 72 hours. CH_2Cl_2 (25 ml) and ice water (20 ml) are added and the organic layer is separated, washed with water containing enough 2N HCl-H_2O to make it acidic. The organic layer is washed with saturated NaCl-H_2O, dried with Na_2SO_4, filtered and evaporated in vacuo to give the crude β-keto ester (1.3 g) which is chromatographed on a SilicAR CC-7 column (30 g). Elution with CH_2Cl_2 (400 ml), 5% ether in CH_2Cl_2 (250 ml), ether (200 ml) in approximately 75 ml fractions gives a total recovery of 927 mg. Fractions 7-10 (5% ether in CH_2Cl_2 eluent) contain 1RS,4RS,5SR-1 methoxy-4-methyl-4-(4-carbethoxy-4,8-dimethyl-5-oxo-8-nonenyl)-3,8-dioxabicyclo[3.2.1]octane (418 mg, 65%).

TLC (10% ether in CH_2Cl_2): R_f = 0.30. IR (neat) 1730 (ester CO), 1709 (keto CO) and 1644 cm^{-1} (olefinic double bond). NMR ($CDCl_3$,δ): 4.67 (m, 2H, $\underline{CH_2}=\overset{\overset{|}{}}{C}-$), 4.17 (q, J=7 Hz, 2H, $-OC\underline{H_2}CH_3$), 3.87 (m, 1H, $H-\overset{\overset{|}{}}{C}-O-$), 3.50 (q, 2H, $-O-\underline{CH_2}-C(O)OCH_3$), 3.40 (s, 3H, $-OC\underline{H_3}$), 1.72 (br s, 3H, $CH_2=\overset{\overset{|}{}}{C}-\underline{CH_3}$), 1.33 (s, 3H, $-CO-\overset{\overset{CO_2^-}{|}}{\underset{\underset{CH_3}{|}}{C}}-$), 1.32 (t, J=7 Hz, 3H, $-OCH_2\underline{CH_3}$), 1.30 (s, 3H, $-\overset{\overset{|}{}}{\underset{\underset{CH_3}{|}}{C}}-O-$).

Example 11

1RS,4RS,5SR-1-Methoxy-4-methyl-4-(4,8-dimethyl-5-oxo-8-nonenyl)-3,8-dioxabicyclo[3.2.1]octane (10)

Aqueous sodium hydroxide (10 ml) is added to the β-keto ester obtained in Example 10 above (2.24 g, 5.7 mM) in methanol (10 ml) with stirring at 2°C under nitrogen. After ten minutes of stirring, the mixture is allowed to come to room temperature and the stirring is continued for four days under nitrogen. The methanol is then evaporated in vacuo and the aqueous residue is extracted with CH_2Cl_2. The CH_2Cl_2 extract is washed with saturated NaCl-H_2O, dried with Na_2SO_4, filtered and evaporated in vacuo to give 1RS,4SR,5SR-1-methoxy-4-methyl-4-(4,8-dimethyl-5-oxo-8-nonenyl)-3,8-dioxabicyclo [3.2.1]octane (1.33 g, 72%).

TLC (10% ether in CH_2Cl_2): R_f = 0.30. IR (neat) 1709 (keto CO), 1658 (double bond), 1060-1090 cm^{-1} (ether bonds). NMR ($CDCl_3$, δ): 4.67 (m, 2H, $\underline{CH_2}=\overset{|}{C}-CH_3$), 3.93 (m, 1H, $\underline{H}-\overset{|}{C}-O-$); 3.50 (q, J=12 Hz, 2H, $-O-\underline{CH_2}-C(O)OCH_3$), 3.37 (s, 3H, $-O\underline{CH_3}$), 1.73 (br s, 3H, $CH_2=\overset{|}{C}-\underline{CH_3}$), 1.32 (s, 3H, $\underline{CH_3}-\overset{|}{C}-O-$), 1.06 (d, J=7 Hz, 3H, $-\overset{|}{C}H-\underline{CH_3}$). GC/MS: M^+ 324; $M-CH_2O$ = 294. BP = 86 ($O-\overset{CH-CH_2}{\overset{|\quad|}{C}}=\overset{|}{C}OCH_3$).

The aqueous basic solution obtained after the separation from the CH_2Cl_2 is cooled to 2°C, stirred, and acidified carefully with ice-cold 6N HCl-H_2O (approximately 3.0 ml). The acidic solution is extracted with CH_2Cl_2 and with ether and the organic extracts are washed separately with NaCl-H_2O, combined, dried with Na_2SO_4, filtered, and evaporated in vacuo to give 1RS,4RS,5SR-1-methoxy-4-methyl-4-(4,8-

dimethyl-5-oxo-8-nonenyl)-3,8-dioxabicyclo[3.2.1] octane-4-carboxylic acid (9b, 0.41 g, 19.6%). TLC (10% ether in CH_2Cl_2): R_f = 0.15 (streak). IR (neat): 3600-3300 (OH), 2800-3550 (OH), 1710 (CO), 1665 cm^{-1}. NMR ($CDCl_3$, δ): 4.67 (m, 2H, $\underline{CH_2}$=C-CH), 3.93 (m, 1H, $\underline{H}$-C-O), 3.50 (q, J=12 Hz, 2H, -O-$\underline{CH_2}$-C(O)OCH_3), 3.42 (s, 3H, -OCH_3), 1.75 (br s, CH_2=C-$\underline{CH_3}$), 1.40 (s, 3H, $\underline{CH_3}$-C-CO_2H), 1.35 (s, 3H, $\underline{CH_3}$-C-O-).

The β-keto acid obtained above (0.41g) is decarboxylated by refluxing it in anhydrous toluene (80 ml) under nitrogen for two hours to give the ketone 1RS,4RS,5SR-1-methoxy-4-methyl-4-(4,8-dimethyl-5-oxo-8-nonenyl)-3,8-dioxabicyclo[3.2.1]octane (0.35 g, 98.4%). This sample of the ketone is identical (TLC, IR, NMR, GC/MS) to the sample of the ketone obtained above.

Example 12

1RS,4RS,5SR-1-Methoxy-4-methyl-4-(5-hydroxy-4,8-dimethyl-8-nonenyl)-3,8-dioxabicyclo[3.2.1]octane (11a)

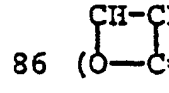
$NaBH_4$ (378 mg, 10 mM) is added in small portions within three minutes to 1RS,4RS,5SR-1-methoxy-4-methyl-4-(4,8-dimethyl-5-oxo-8-nonenyl)-3,8-dioxabicyclo[3.2.1] octane (1.33 g, 4.1 mM) in absolute ethyl alcohol (10 ml) while stirring at 0°C under nitrogen. The mixture is stirred in the cold for two hours and then added dropwise to ice water (15 ml) with stirring. The aqueous mixture is carefully acidified with 6N HCl-H_2O and the acidic solution is extracted with ether (3x30 ml). The extract is washed with saturated NaCl-H_2O (10 ml) containing a few drops of saturated $NaHCO_3$-H_2O to make it basic. The ether is evaporated in vacuo and the residue is dissolved in CH_2Cl_2, washed with NaCl-H_2O, dried with Na_2SO_4, filtered, and evaporated in vacuo to give 1RS,4RS,5SR-1-methoxy-4-methyl-4-(5-hydroxy-4,8-dimethyl-8-nonenyl)-3,8-dioxabicyclo[3.2.1]octane (1.25 g, 93.5%).

TLC (ether): R_f = 0.76
IR (neat): 3350 (OH), 1090-1060 cm^{-1} (ether bonds). NMR ($CDCl_3$, δ): 4.68 (br s, 2H, $\underline{CH_2}=C(CH_3)$), 3.91 (m, 1H, $\underline{H}-C(CH_3)(CH_2)-O-$), 3.5 (q, J=11 Hz, 2H, $-O-\underline{CH_2}-C(CH_3)(CO_2CH_3)$), 3.38 (s, 3H, $-O\underline{CH_3}$), 1.72 (br s, 3H, $CH_2=C(CH_3)-\underline{CH_3}$), 1.31 (s, 3H, $-O-C(CH_3)(CH_2)-\underline{CH_3}$), 1.18 (d, J=7 Hz, 1H, $-CH-\underline{CH_3}$). GC/MS of TMS derivative (C.I. mode): $(M+1)^+$ = 399, 399 - TMSO = 310 (BP).

Example 13

1RS,4RS,5SR-1-Methoxy-4-methyl-4-(5-acetoxy-4,8-dimethyl-8-nonenyl)-3,8-dioxabicyclo[3.2.1]octane (11b)

A mixture of anhydrous pyridine (1.5 ml) and acetic anhydride (3.0 ml) is added to the ketal alcohol (1.25 g, 3.83 mM) obtained in Example 12 above at room temperature under nitrogen. The mixture is stirred at room temperature for sixteen hours after which the solution is evaporated while stirring under high vacuum at 45°C for one hour. The residue obtained is dissolved in CH_2Cl_2 and the resulting solution is washed with saturated NaCl-H_2O containing 2N HCl-H_2O. The solution is then washed with saturated NaCl-H_2O, dried with Na_2SO_4, filtered and evaporated in vacuo to give 1RS,4RS,5SR-1-methoxy-4-(5-acetoxy-4,8-dimethyl-8-nonenyl)-3,8-dioxabicyclo [3.2.1]octane (1.4 g, 99.3%).

TLC (10% ether in CH_2Cl_2): R_f = 0.65. IR (neat): 1739 (CO), 1242 (acetate), 1090-1030 cm^{-1} (ether bonds). NMR ($CDCl_3$, δ): 4.68 (br, 3H, $\underline{CH_2}=C(CH_3)$ and $-\underline{CH}-OCOCH_3$), 3.91 (m, 1H, $\underline{H}-C(CH_3)(CH_2)-O-$), 3.5 (q, J=11 Hz, 2H, $-O-\underline{CH_2}-C(O)OCH_3$), 3.38 (s, 3H, $-O\underline{CH_3}$), 2.03 (s, 3H, $-OCO\underline{CH_3}$), 1.72 (br s, 3H, $CH_2=C(CH_3)-\underline{CH_3}$), 1.31 (s, 3H, $\underline{CH_3}-C(CH_3)(CH_2)-O-$), 1.18 (d, J=7 Hz, 3H, $-CH-\underline{CH_3}$). GC/MS: M^+ 368, M-CH_2O = 338, M - HOAc = 308, BP = 86  .

Example 14

1RS,4RS,5SR-1-Hydroxy-4-methyl-4-(5-acetoxy-4,8-dimethyl-8-nonenyl)-3,8-dioxabicyclo[3.2.1]octane (12)

1N HCl-H_2O (4 ml) is added to 1RS,4RS,5SR-1-methoxy-4-(5-acetoxy-4,8-dimethyl-8-nonenyl)-3,8-dioxabicyclo [3.2.1]octane (1.4 g, 3.8 mM) in acetone (12 ml). The mixture is stirred and heated at 55°C for four hours. The acetone is evaporated in vacuo at room temperature, the residue is extracted with CH_2Cl_2 and washed with saturated NaCl-H_2O containing enough saturated NaHCO -H_2O to make it basic, and then with NaCl-H_2O. The solution is dried with Na_2SO_4, filtered, and evaporated in vacuo to give 1RS,4RS,5SR-1-hydroxy-4-methyl-4-(5-acetoxy-4,8-dimethyl-8-nonenyl)-3,8-dioxabicyclo[3.2.1] octane (1.23 g, 91.4%).

TLC (10% ether in CH_2Cl_2): R_f = 0.15. IR (neat) 333 (OH), 1725 (CO), 1242 cm^{-1} (acetate). NMR ($CDCl_3$,δ): 4.80 (m, 1H, $\underline{H}$-$\dot{C}$-$OCOCH_3$), 4.72 (br, 2H, $\underline{CH_2}$=C-CH_3), 3.97 (m, 1H, $\underline{H}$-$\dot{C}$-O-), 3.58 (q, 2H, -O-$\underline{CH_2}$-$\dot{C}$(O)OCH_3), 2.07 (s, 3H, -O-CO-$\underline{CH_3}$), 1.75 (br s, 3H, CH_2= $\dot{C}$-$\underline{CH_3}$), 1.35 (s, 3H, $\underline{CH_3}$-$\dot{C}$-O-), 0.87 (d, J=7 Hz, 3H, -CH-$\underline{CH_3}$). GC/MS of TMS derivative: M^+ (426 $\xrightarrow[-HOAc]{}$ 366; 366-CH_2O = 336; 336 - CH_2 = $C(CH_3)CH_2\dot{C}H_2$ = 267. BP = 73 (TMS).

Example 15

Ethyl(1RS,4SR,5RS)-4-(5-acetoxy-4,8-dimethyl-8-nonenyl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetate (13)

(Carbethoxymethylene)triphenylphosphorane (3.6 g, 10.3 mM) is added to 1RS,4RS,5SR-1-hydroxy-4-methyl-4-(5-acetoxy-4,8-dimethyl-8-nonenyl)-3,8-dioxabicyclo [3.2.1]octane (1.23 g, 3.47 mM). The mixture is heated under nitrogen to 120°C, stirred at this temperature for two days and then cooled to room temperature after which additional Wittig reagent

(1.2 g, 3.4 mM) is added. The mixture is heated again under nitrogen to 120°C and stirred at this temperature for two more days. The reaction mixture is then cooled to room temperature and extracted with a mixture of ether and hexane six times (1 ml ether and 20 ml hexane, each time). The combined extracts are evaporated in vacuo to give an oil (1.92 g). The crude reaction product is treated with petroleum-ether (30 ml of BP 30-60°C and filtered through Celite to give ethyl (1RS,4SR,5RS)-4-(5-acetoxy-4,8-dimethyl-8-nonenyl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetate (10.0 g, 68.7%).

TLC (10% ether in CH_2Cl_2): R_f = 0.40.

IR (neat) 1725 (CO), 1242 cm^{-1} (acetate).

NMR ($CDCl_3$, δ): 4.83 (m, 1H, $-\underset{\underline{H}}{\underline{\dot{C}}}-OCOCH_3$), 4.67 (m, 2H, $\underline{CH_2}=\underline{\dot{C}}-CH_3$), 4.13 (q, J=7 Hz, 2H, $-COO\underline{CH_2}CH_3$), 3.83 (m, 1H, $\underline{H}-\underset{\underline{O}}{\underline{\dot{C}}}-$), 3.58 (q, J=11 Hz, 2H, $-O-\underline{CH_2}-\dot{C}(O)CH_2-$), 2.60 (s, 2H, $-O-\underline{\dot{C}}-\underline{CH_2}-CO_2C_2H_5$), 2.03 (s, 3H, $-O-\underline{CH_3}$), 1.72 (br s, 3H, $CH_2=\underline{\dot{C}}-\underline{CH_3}$), 1.30 (s, 3H, $-\underset{\underline{CH_3}}{\underline{\dot{C}}}-O-$), 1.25 (t, J=7 Hz, 3H, $-COOCH_2\underline{CH_3}$), 0.88 (d, J=7 Hz, 3H, $-\underline{\dot{C}}H-\underline{CH_3}$).

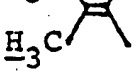
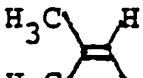
A sample (264 mg) is further purified by chromatography on SilicAR CC-7 (2.0 g). Elution with CH_2Cl_2 (500 ml) gives the faster running impurities (25 mg). Elution with 3% ether in CH_2Cl_2 (500 ml) gives ethyl (1RS,4SR,5RS)-4-(5-acetoxy-4,8-dimethyl-8-nonenyl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetate (89.1 mg, 35%).

Example 16

Ethyl(1RS,4SR,5RS)-4-(5-acetoxy-4,8-dimethyl-7-nonenyl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetate (14)

p-Toluenesulfonic acid monohydrate (8.2 mg) is added to benzene (12 ml). The mixture is stirred and refluxed in a Dean-Stark apparatus and some of the benzene (4 ml) is drained from the side-arm. The bicyclic acetoxy ester, ethyl(1RS,4SR,5RS)-4-(5-acetoxy-4,8-dimethyl-8-nonenyl)-4-methyl-3,8-dioxabicyclo[3.2.1] octane-1-acetate (85 mg, 0.2 mM), dissolved in benzene (6 ml), is added at room temperature to the above mixture and the resultant mixture is stirred and refluxed (bath at 130°C) for two hours. The temperature of the heating bath is then lowered to 90°C and the stirring is continued at 90°C for sixteen hours and then at room temperature for seventy-two hours. The reaction mixture is added to saturated $NaHCO_3$-H_2O (10 ml) and ether (20 ml). The organic layer is separated, washed with saturated NaCl-H_2O, dried with Na_2SO_4, filtered, and evaporated in vacuo to give ethyl(1RS,4SR,5RS)-4-(5-acetoxy-4,8-dimethyl-7-nonenyl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetate (80.4 mg, 95%).

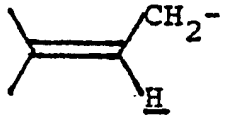
TLC (10% ether in CH_2Cl_2): R_f = 0.4.

IR (neat) 1724 (CO), 1242 (acetate), 1087 1060, 1020 cm^{-1} (ether bonds). NMR ($CDCl_3$, δ): 5.12 (t, 1H, $\rangle C=\underset{H}{C}-$), 4.13 (q, J=7 Hz, 2H, $-COO\underline{CH_2}CH_3$), 3.90 (m, 1H, $\underline{H}-\overset{|}{C}-O-$), 3.58 (q, J=11 Hz, 2H, $-O-\underline{CH_2}-\overset{|}{C}(O)CH_2-$), 2.65 (s, 2H, $-O-\overset{|}{C}-\underline{CH_2}-CO_2C_2H_5$), 2.03 s, 3H, $-O-CO-\underline{CH_3}$), 1.75 (br s, 3H, ), 1.67 (br s, 3H, ), 1.35 (s, 3H, $-\overset{|}{C}(\underline{CH_3})-O-$), 0.92 (d, J=7 Hz, 1H, $-CH-\underline{CH_3}$). GS/MS (C.I. mode) $(M+1)^+$ 425 $\xrightarrow{-HOAc}$ 365 (base peak).

Example 17

1RS,4SR,5RS-4-(4,8-dimethyl-5-hydroxy-7-nonen-1-yl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetic acid (I)

2N NaOH-H_2O (2.0 ml) is added to ethyl (1RS,4SR, 5RS)-4-(5-acetoxy-4,8-dimethyl-7-nonenyl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetate (79 mg, 0.19 mM) in methanol (2.0 ml) while stirring under nitrogen at 2°C. After ten minutes of stirring, it is allowed to come to room temperature and stirred under nitrogen for seventy-two hours. The methanol is evaporated *in vacuo* at room temperature and the residue is extracted with ether. The aqueous basic solution is cooled with ice water, stirred, and acidified with 6N HCl-H_2O, and extracted with ether. It is washed with saturated NaCl-H_2O, dried with Na_2SO_4, filtered, and evaporated *in vacuo* to give 1RS,4SR,5RS-4-(5-hydroxy-4,8-dimethyl-7-nonenyl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetic acid (66.9 mg, 91.3%).

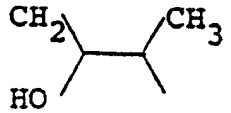
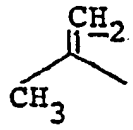
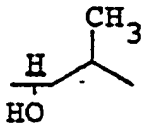
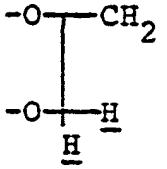
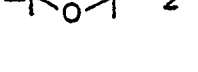
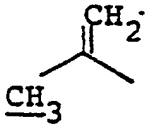
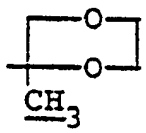
TLC ether: petroleum-ether-AcOH (20:5:05): R_f = 0.57. IR (neat) 3500-3300, 2500-2300 (OH), 1720 (CO, 1090, 1050, 1010 cm^{-1} (ether bonds). NMR ($CDCl_3$, δ): 5.43 (br m, 2H, -O<u>H</u> + -CO_2<u>H</u>), 5.12 (t, 1H, ), 3.90 (m, 1H, <u>H</u>-C-O-), 3.58 (q, J=11 Hz, 2H, -O-<u>CH_2</u>-C(O)CH_2-), 3.33 (m, 1H, -C<u>H</u>-OH), 2.65 (br s, -<u>CH_2</u>-CO_2H), 1.75 and 1.67 (2 x br s, 2 x 3H, vinyl methyls), 1.35 (s, 3H, -C(<u>CH_3</u>)-O-), 0.92 (d, J= Hz, 3H, -CH-<u>CH_3</u>). GC/MS of bis-TMS derivative M^+ 498; M-C_5H_9 = 429; M-C_5H_9-TMSOH = 339; BP = 73.

Example 18

(1RS,4SR,5RS)-4-(5-Hydroxy-4,8-dimethyl-8-nonenyl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetic acid Monohydrate (16)

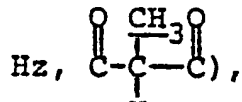
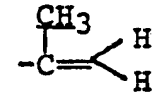
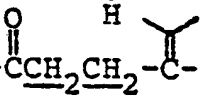
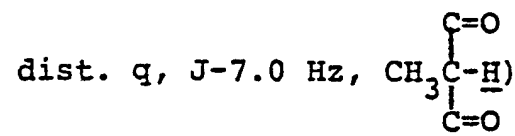
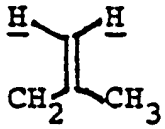
2N NaOH-H_2O (5.0 ml) is added to ethyl (1RS,4SR,5RS)-4-(5-acetoxy-4,8-dimethyl-8-nonenyl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetate (1.06 g, 2.5 mM) in methanol (5.0 ml) while stirring at 0°C under nitrogen. The cooling bath is removed after fifteen minutes and the reaction is stirred at room temperature for three days. The methanol is evaporated in vacuo at room temperature and the residue is extracted with ether. The aqueous basic solution is cooled with ice water, stirred, acidified with 6N HCl-H_2O, and extracted with ether. This extract is washed with saturated NaCl-H_2O, dried with Na_2SO_4, filtered, and evaporated in vacuo to give 608 mg (68.7%) of crude acid, which is purified by column chromatography on SilicAR CC-7. The acid is eluted with a mixture of petroleum ether and ether and acetic acid = 150 + 50 + 1 ml; 200 + 200 + 2 ml; and 150 + 50 + 1 ml to give (1RS,4SR,5RS)-4-(5-hydroxy-4,8-dimethyl-8-nonenyl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1 acid (305 mg).

IR ($CHCl_3$): 3000, 2800-2500 (shld), 1750, 1720, 1650, 730 cm^{-1}.

NMR ($CDCl_3$): 6.10 (m, 2H, $CO_2\underline{H}$ and ), 4.70 (m, 2H, ), 3.86-3.31 (m, 4H,  ,  and ), 2.63 (m, 2H, $\underline{CH_2}$-CO_2H), 1.71 (br s, 3H, ), 1.30 (s, 3H, ), 0.88 (d, J=6 Hz, 3H, -CH$\underline{CH_3}$-).

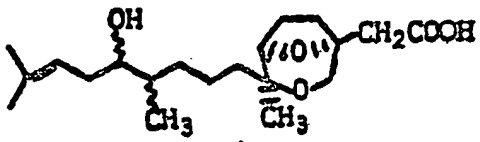
Preparation of ethyl 2,6-dimethyl-3-oxo-6-heptenoate

Sodium hydride (50% in mineral oil (7.68 g, 0.155 M) is treated with hexane to remove the mineral oil and suspended in tetrahydrofuran (300 ml). The suspension is cooled to +2°C in an ice bath and to it is added dropwide ethyl 2-methylacetoacetate (22.8 ml, 0.158 M). Ten minutes after the addition is complete, n-butyllithium (2.4 M in hexane; 66.4 ml, 0.15 M) is added at +2°C. Ten minutes after this addition is complete, methallyl chloride (16 ml, 0.159M) is added. The solution is stirred at 0°C for ten minutes, acidified with 6N $HCl-H_2O$ and extracted with ether. The ether layer is separated and washed with saturated $NaCl-H_2O$, dried with Na_2SO_4, and the solvent evaporated *in vacuo* to afford a yellow oil. Fractional distillation affords 10.1 g (57%, based on recovered ethyl 2-methylacetoacetate) of ethyl 2,6-dimethyl-3-oxo-6-heptenoate as a colorless oil, BP 83-85°C/1 mm.

IR (neat): 3080, 2980, 2960, 2900, 1745, 1725, 1650, 1450, 1180, 870 cm^{-1}. NMR ($CDCl_3$, δ): 1.27 (3H, t, J=7, $\underline{CH_3}-H_2O$); 1.37 (3H, d, J=7.0 Hz, ), 1.73 (3H, br s, ), 2.06-2.85 (4H, M, ), 3.53 (1H, dist. q, J-7.0 Hz, ), 4.16 (2H, q, J=7.0 Hz, $O\underline{CH_2}-CH_3$), 4.70 (2H, m, ).

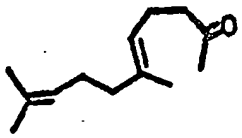
Claims:

1. The process for the preparation of a compound of the formula

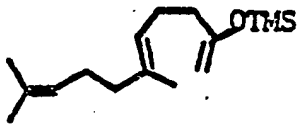


and/or a compound according to Claim 13

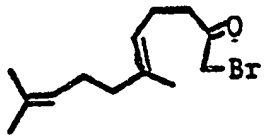
which comprises reacting a compound of the formula



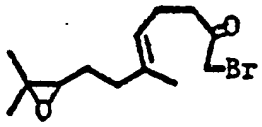
with trimethylsilyl chloride to form an enol silylether of the formula



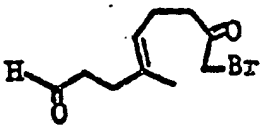
reacting the enol silylether with a brominating agent to form a bromide of the formula



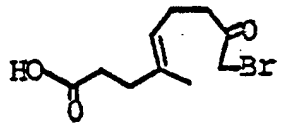
reacting the compound formed with a peroxy acid to form an epoxide of the formula



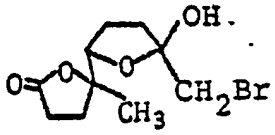
reacting the epoxide with periodic acid to form an aldehyde of the formula



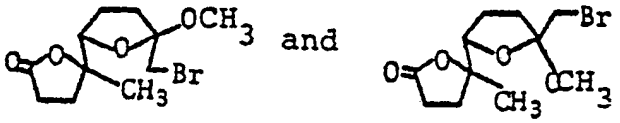
reacting the aldehyde with an oxidizing agent to form an acid of the formula



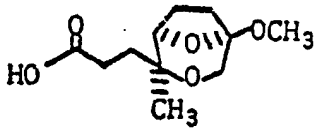
reacting the acid formed with a peroxy acid to form a bromo hemiketal γ-lactone of the formula



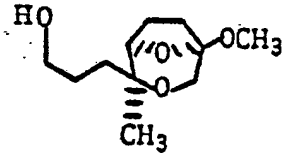
reacting the bromo hemiketal γ-lactone with a trialkyl orthoformate to form a mixture of the cis/trans-bromo ketal lactone of the formula



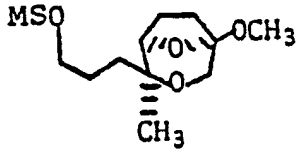
cyclizing the cis bromo ketal lactone with a cyclizing agent to form a bicyclic ketal acid of the formula



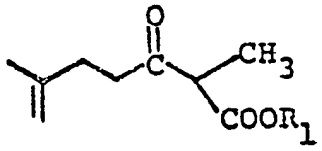
reacting the ketal acid with a first reducing agent to form an alcohol of the formula



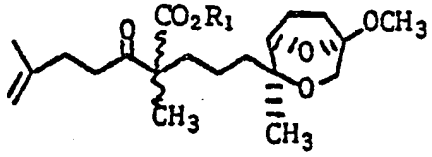
reacting the alcohol with methanesulfonyl chloride to form a mesylate of the formula



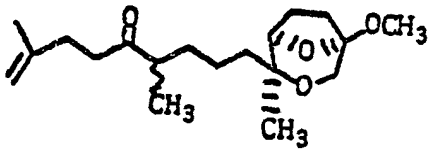
reacting the mesylate with a compound of the formula



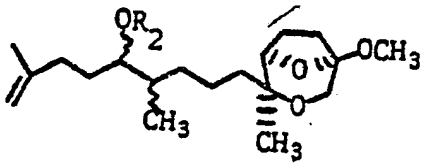
to form a condensation product of the formula



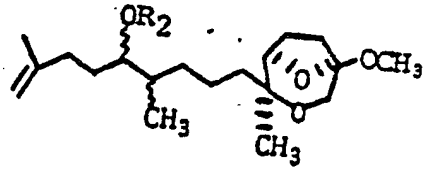
hydrolyzing and decarboxylating the carboxylic ester with a decarboxylating agent to form a ketone of the formula



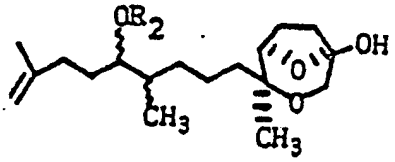
reducing the ketone with a second reducing agent to form an alcohol of the formula



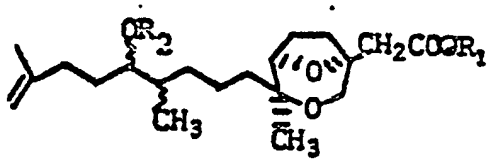
esterifying the alcohol with an esterifying agent to form an ester of the formula



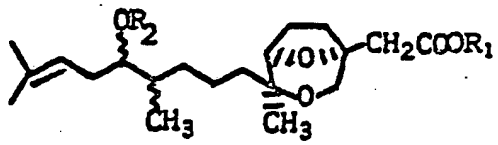
reacting the ketal with acid to form a hemiketal of the formula



reacting the hemiketal with (carbethoxymethylene)triphenylphosphorane to form a compound of the formula



isomerizing the 8-nonenyl ester with an isomerizing agent to form a 7-nonenyl ester of the formula



at least one of
and hydroxyzing/the esters with a hydrolyzing agent, wherein R_1 is hydrogen or a lower alkyl group having 1-5 carbon atoms, R_2 is hydrogen or lower acyl having 2-5 carbon atoms, TMS is a trimethylsilyl group and MS is a methylsulfonyl group.

2. The process of Claim 1 wherein the brominating agent is N-bromosuccinimide.

or Claim 2
3. The process of Claim 1/wherein the oxidizing agent is CrO_3-H_2SO_4.

any one of to 3
4. The process of/Claims 1/wherein the peroxy acid is m-chloroperbenzoic acid.

any one of to 4
5. The process of/Claims 1/wherein the cyclizing agent is potassium hydroxide.

any one of to 5
6. The process of/Claims 1/wherein the first reducing agent is diborane.

any one of to 6
7. The process of/Claims 1/wherein the hydrolyzing and decarboxylating agent is sodium hydroxide.

8. The process of /Claims any one of 1 to 7/ wherein the second reducing agent is sodium borohydride.

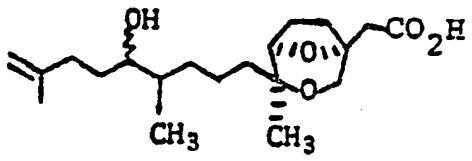
9. The process of /Claims any one of 1 to 8/ wherein the esterifying agent is acetic anhydride.

10. The process of /Claims any one of 1 to 9/ wherein the acid is hydrochloric acid.

11. The process of /Claims any one of 1 to 10/ wherein the isomerizing agent is p-toluenesulfonic acid.

12. The process of /Claims any one of 1 to 11/ wherein the hydrolyzing agent is sodium hydroxide.

13. A compound of the formula



14. A compound according to Claim 13, or a composition comprising a compound according to Claim 13 and a pharmaceutically acceptable carrier, for use as a contragestational agent.

European Patent Office

EUROPEAN SEARCH REPORT

0039595
Application number
EP 81 30 1934

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
D	US - A - 4 102 895 (ORTHO)	13,14

CLASSIFICATION OF THE APPLICATION (Int. Cl.³)

C 07 D 493/08
A 61 K 31/34//
C 07 F 7/18
C 07 C 49/227
C 07 D 303/08
C 07 C 49/258
59/88
C 07 D 307/32
C 07 C 59/76
(C 07 D 493/08
319/00
307/00)

TECHNICAL FIELDS SEARCHED (Int. Cl.³)

C 07 D 493/08
A 61 K 31/34

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	06-08-1981	ALFARO

EPO Form 1503.1 06.78